ANTI GANGLIOSIDE ANTIBODY PROFILE IN GBS - CLINICAL, IMMUNOLOGICAL AND NEUROPHYSIOLOGICAL SIGNIFICANCE

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CERTIFICATE

This is to certify that the dissertation entitled **"ANTI GANGLIOSIDE ANTIBODY PROFILE IN GBS - CLINICAL, IMMUNOLOGICAL AND NEUROPHYSIOLOGICAL SIGNIFICANCE "** is a bonafide work done by **Dr. VENKATESH . P** at Madras Medical College, Chennai in partial fulfilment of the university rules and regulations for award of D.M., Degree in NEUROLOGY (Branch-I) under my guidance and supervision during the academic year 2011 -2014.

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DECLARATION

I solemnly declare that this dissertation entitled "**ANTI GANGLIOSIDE ANTIBODY PROFILE IN GBS - CLINICAL, IMMUNOLOGICAL AND NEUROPHYSIOLOGICAL SIGNIFICANCE"** was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, during 2011-2014 under the guidance and supervision of **Prof.R.LAKSHMI NARASIMHAN M.D,D.N.B(Med),D.M,D.N.B(Neuro)**. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of D.M. Degree in Neurology (Branch I).

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ABSTARCT

Guillain-Barre´ syndrome (GBS) is an acute onset, monophasic, paralytic disorder of the peripheral nervous system. The patho physiology of GBS involves an auto immune mediated attack on glycolipid components of nerves which has been supported by the frequent rise of anti ganglioside antibodies in acute sera of GBS patients. Anti ganglioside antibodies of IgG type, are found to be elevated in the sera from almost 60% of GBS patients. These anti ganglioside antibodies can be used for early detection of GBS because of their presence in the acute phase sera. Thereby they can be used as diagnostic markers of various GBS subtypes.It has been demonstrated that these antiganglioside antibodies are associated with poor prognosis in some studies. By conducting this study,we aimed to investigate the value of anti ganglioside antibody detection as a diagnostic and prognostic marker of GBS in acute phase. This study extends the previous findings on the relationship between antiganglioside antibodies and GBS. Though many studies on this topic are available from western countries, very few have been done in our country. Among the available studies , number of patients included in the study was low with occasional case reports of sero positivity. To overcome these limitations, this study was done to assess the anti ganglioside antibody positivity in GBS patients and its correlation with

disease severity.From our study, we found out the following conclusions,

- Assessment of antiganglioside antibody profile in GBS helps in the detection of disease in the early phase of illness.
- Antiganglioside antibodies are useful in prognostication of GBS.
- Antiganglioside antibodies are invariably present in severe GBS.
- Larger sample size is required to make any definite meaningful correlation and utility of these antiganglioside antibodies in GBS.

INTRODUCTION

Guillain-Barre´ syndrome (GBS) is an acute onset, monophasic, paralytic disorder of the peripheral nervous system. The term GBS is usually considered to be synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but with the growing recognition over the past few decades of variants, the diseases which fall under the rubric GBS has developed to include axonal variants and few restricted variants like Miller Fisher syndrome (MFS).[1,2] The clinical characteristics of Guillian Baare syndrome were documented by Landry in 1859.[3] After few decades Guillain, Barre´, and Strohl demonstrated the distinctive CSF characteristics of albumino cytological dissociation. The typical pathological findings of this illness including the peripheral nerve inflammatory changes had been described by Haymaker and Kernohan in 50 GBS patients.[4] Waksman and Adams in their animal experiments demonstrated allergic neuritis in by injecting the peripheral nerve tissue with Freund adjuvant in the mid 1950s. Plasma exchange was found as an efficacious treatment option for GBS in 1980s.[5,6] In1990s, efficacy of intravenous immunoglobulin (IVIg) in GBS was demonstrated.[7,8]

The incidence of GBS has been reported as one to two per one lakh population. The general population had been shown to acquire the risk of GBS by one in thousand. GBS equally affects males and females. This disease can occur in

any age.[9,10] The onset of GBS is usually preceded by infectious illness. It usually has been shown to occur 10 – 14 days prior to the starting of GBS symptoms.[11] Among the antecedent infections, most commonly reported organisms are Campylobacter jejuni, Epstein-Barr virus, cytomegalovirus (CMV), influenza virus and Mycoplasma pneumonia. In addition to these infections, GBS has also been found to associated with immunization, surgery and parturition .[12]

The patho physiology of GBS involves an auto immune mediated attack on glycolipid components of nerves which has been supported by the frequent rise of anti ganglioside antibodies in acute sera of GBS patients. The antecedent microbial agents have epitopes on their surface which are similar to epitopes on the peripheral nerves resulting in the peripheral nerve components. Molecular mimicry between microbial and self antigens has been postulated as a pathogenic mechanism to account for the specific immune responses in postinfectious GBS.[13] Carbohydrate components of gangliosides found on the peripheral nerve surface are molicular mimics of the lipooligosaccharides of Campylobacter jejuni.[14,15] During an otherwise mild infection , the antibodies which are meant to remove the microbial agents attach to carbohydrate component of nerves, causing injury to the peripheral nerves.[16] The major sites of antibody attacks are the paranodal myelin, presynaptic component of the neuromuscular junction and the exposed axolemma at nodes of Ranvier.[11] Macrophage induced destruction of myelin covering

occurs.[3,16] Though the injury to myelin may affect the entire length of the nerve, the earliest pathological changes are seen at places where there is presence of the week blood-nerve barriers.[11,17] The pathogenic mechanism of axonal injury is thought to be due to complement activation causing membrane attack complex production causing disintegration of the end portion of axon.[11]

The pathological features vary according to the clinical variants of GBS. In AIDP,the characteristic pathologic picture has been completely known for more than 30 years, and is marked predominantly by inflammatory demyelinatory changes with focal and diffuse infiltration by lymphocytes and lipid-laden macrophages. Though the major burden of disease tends to drop on the motor roots with the adjacent proximal plexuses, sensory motor nerve fibers also show some pathological changes. The earliest visible change in myelinated nerve fibers is the outer myelin layer vacuolation , which is preceded by activation of complement components along the complete outer Schwann cell surface of affected nerve fibers.It has been speculated that complement components get activated by antibody attachment to epitopes on the outer membrane of Schwann cells which leads to the complement activation initiating the cycle of myelin vacuolation,disintegration and ultimately phagocytosis by macrophages. Lymphocytic infiltration appear later in the pathological process. The degree of

secondary axonal degeneration depends on the intensity of the inflammatory changes. [18]

In contrast, the pathology of both AMAN and AMSAN variant of GBS is characterized by the absence of inflammatory changes. The major effect on nerve fibers is degeneration of axons, but the severity of pathologic change is variable. In AMAN variant of GBS, the primary immune attack is on the motor nodes of Ranvier.The pathological changes are also seen in motor roots, peripheral nerves, and also in the intramuscular motor twigs. It has been proved that the distal pathology alone can explain majority of the clinical and electrophysiological characteristics of acute motor axonal neuropathy.[19,20]

In AMSAN variant of GBS, the primary attack is on both the motor and sensory nerve nodes of Ranvier, but the sequence of pathological events leading to complement activation, macrophage infiltration and the axonal damage follow the similar chain as in acute motor axonal neuropathy variant of GBS.[19,20,21]

The GBS is clinically characterized by abrupt onset sensory symptoms. These sensory manifestations are often accompanied by or immediately followed by dysfunction of power. Patients are able to note the exact date of onset of motor and sensory dysfunction. The illness is characterized by its rapid progression, with around half of affected persons progressing to the clinical peak by approximately two weeks and around ninety percent of patients reach the nadir by about four

weeks. Neurological examination shows both distal and proximal weakness of symmetrical distribution. There may not be any sensory signs initially. Generalized absent or reduced jerks is the major neurological feature of the illness. Phrenic nerve involvement leading to diaphragmatic paralysis is also common. Around 30 % GBS patients need respiratory support as a result of oropharyngeal or neuromuscular weakness.[22-27] Autonomic disturbances in the form of tachycardia is seen in approximately 50 % of GBS patients. Though less common, more serious autonomic disturbances such as severe cardiac arrhythmias, labile blood pressure and gastrointestinal motility related complications may occur.[28-32]

CSF analysis and electrophysiological studies serve as supportive ancillary tests for GBS.Both these tests don't show any abnormal response initially. The restrictions of these supportive tests at the starting combined with the significance of timely intervention of GBS urges that the physician at times formulate the diagnosis based mainly on history and clinical details. The raised CSF protein content and acellular smear known as albumin cytological dissociation is seen on CSF studies in half of patients; whereas, elevated CSF protein content occurs in more than 90% of GBS patients at clinical nadir. CSF analysis need not be repeated if the first CSF analysis is normal with clearcut clinical possibility of GBS. CSF with cellular smear is not the feature of GBS . This feature may occur in

infectious (AIDS, Cytomegalovirus, Lyme), neoplastic, or sarcoidosis with polyradiculoneuropathy.[23]

Electrophysiological studies such as nerve conduction studies are done to keep up the clinical diagnosis that the acute weakness is because of peripheral nerve involvement. Nerve conduction study of GBS patients often shows demyelination findings, such as markedly reduced conduction velocity, and prolonged CMAP latency and F-wave latency prolongation.[33] Electrophysiological characteristics of acquired demyelination such as temporal dispersion ,conduction block, non uniform conduction velocity slowing) are predominantly helpful as these findings are distinctive of acquired demyelinating neuropathies of immune dysregulation. In early phase of GBS, prolonged F wave latencies are characteristically seen followed by prolonged distal CMAP latency with temporal dispersion .Whereas reduced nerve conduction velocities and conduction block are usually late signs in electrophysiological study of GBS. Another electrophysiological characteristic of this illness is ‘‘sural sparing’’; that is, the presence of a normal sural study in the presence of deranged upper limb sensory study. The sural sparing pattern is found in approximately 50-75 % of GBS patients done at the initial phase of illness. This characteristic pattern is highly unusual for neuropathies except GBS. In addition to these electro physiological features, other features consist of absent H-reflexes, reduced distal CMAP

amplitudes. It has been shown that the H-reflex was characteristically absent in 97% of GBS patients in the first week of illness. It should also be noted that motor nerve conduction findings are more often abnormal than that of sensory nerve study in early GBS. Blink reflex is usually abnormal in GBS patients with facial nerve involvement. Needle electromyography typically shows the feature of reduction in motor unit action potential recruitment. [34-36]

Magnetic resonance imaging spine is not routinely indicated. However, it is mainly done to rule out other mimics, such as myelopathy or compressive and infiltrative lesions. Presence of enhancement of affected root and cranial nerve on MRI support the diagnosis of GBS.[37-39]

Plasmaphresis and intravenous immunoglobulins are effective treatment options for GBS if given during the initial few weeks of illness. In GBS, plasma exchange is given as 50 mL/kg, on 5 cycles over one to two weeks.[6,7,8] AAN guidelines stated that plasma exchange accelerate recovery in immobile patients with GBS who take treatment within 1 month of disease onset, and that plasma exchange accelerate recovery of mobile GBS patients who are examined within 14 days. Therefore, AAN recommends plasma exchange for immobile GBS patients within 1month and for mobile GBS patients within 2 weeks of disease onset.[40] The most advantageous number of PEs is not known, but many clinicians use the North American protocol which uses 200 to 250 mL/kg over 7 to 10 days. One study

showed that for adult GBS patients with mild illness, 2 exchanges were superior than none; and for patients with moderate illness or severe illness (on ventilator), 4 exchanges were better than 2 and 6 exchanges were no superior than four. It has been demonstrated that the antiganglioside antibody levels fall after the first 2 plasma cycles but not with further cycles.[41]

Although both these treatment options are mostly of similar efficacy, some studies have shown speed recovery with IVIg treatment when compared to plasma exchange. For both older & childhood GBS cases , intravenous immunoglobulin is given as two gram per kg total dose divided over two to five days. The American academy of neurology guidelines concluded that IVIg is similarly effective in fastening recovery for GBS patients who require aid to walk if intravenous immunoglobulin is given within 2 weeks of the disease onset. The AAN guidelines recommend treatment with intravenous immunoglobulin for GBS patients who need aid to walk within two weeks or four weeks of GBS disease symptom onset.[40]

Anti ganglioside antibodies of IgG type, are found to be elevated in the sera from almost 60% of GBS patients.[42,43,44] These anti ganglioside antibodies can be used for early detection of GBS because of their presence in the acute phase sera. Thereby they can be used as diagnostic markers of various GBS subtypes.It has been demonstrated that these antiganglioside antibodies are associated with poor prognosis in some studies. By conducting this study,we aimed to investigate

the value of anti ganglioside antibody detection as a diagnostic and prognostic marker of GBS in acute phase.

REVIEW OF LITERATURE

Guillain-Barré syndrome (GBS) was initially described in detail in 1859, by Jean Baptiste Landry, a French physician. However, Guillain, Barré, and Strohl gave the first widespread description, including clinical features,pathologic features and cerebrospinal fluid features. Additional information of similar cases were followed in detail. In 1949 a detailed clinicopathologic note of fifty cases of severe areflexic paralysis demonstrated that the clinical features may correlate with demyelinating or axonal changes.[4] It is now obvious that Guillain-Barré syndrome is a syndrome which consists of several specific diseases,including the demyelinating form, namely acute inflammatory demyelinating polyneuropathy and axonal forms consists of acute motor axonal neuropathy and acute motor and sensory axonal neuropathy. Other clinical variants include the Miller Fisher syndrome characterized by the triad of ataxia ,ophthalmoplegia and areflexia, oropharyngeal variant, pure sensory neuropathy/ neuronopathy, pandysautonomia, and overlap syndromes.[2,45]

The incidence of Guillain-Barré syndrome in Europe and North America is1-2/100,000/year in adults, and 0.4–1.4/100,000/year in children. Annual incidence of GBS from other regions ranges from as low as 0.40/100,000 in Brazil to 2.5/ 100,000 in Curacao.[46,47,48] In particular, the relative frequency of axonal

type in comparison with the demyelinating variant varies by location. In North America and Europe, acute inflammatory demyelinating polyneuropathy is the major form, reporetd in up to 90% of Guillain-Barré syndrome patients.[49] In contrast, axonal types account for 40 to 60% of patients in Asian countries.[50,51] In North America, Miller Fisher syndrome is rare, accounting for 1 to 7% of all Guillain-Barré syndrome patients, but in Taiwan and Japan it is very common, accounting for even up to 19% of GBS patients.[52,53,54,55] Around fifty percent of GBS patients have an precedent infection, usually less than 4 weeks prior to disease onset. The most common infections reported to be associated with GBS in adults are gastrointestinal (6–26%) and respiratory (22–53%) infections. Antecedent infections are usually more common in children (67–85%) with a larger frequency of respiratory (50–70%) than gastrointestinal (7–14%).The most commonly recognized organisms include Campylobacter jejuni, Epstein–Barr virus ,Cytomegalovirus and Mycoplasma pneumoniae.[46,49] Most cases of Guillain-Barré syndrome are sporadic, although rare epidemics have been noted after bacterial enteritis.[48]

The initial manifestations of the GBS are numbness, pain, paresthesia, weakness or some mixture of these symptoms. The major feature is progressive bilateral and relatively symmetric limb weakness, and the weakness increases over a period of twelve hours to 28 days before reaching a plateau. Patients

characteristically have generalized absent or diminished reflexes.Among the available clinical diagnostic criteria Modified Asbury Cornbloth criteria is commonly used and is depicted in table 1.[22] A history of symptoms suggestive of upper respiratory or gastrointestinal infection three days to six weeks prior to the disease onset is not uncommon.[56]

The differential diagnosis of GBS is wide, and detailed neurologic examination localizes the illness to the peripheral nerves.The presence of distal paresthesia increases the possibility that the likely diagnosis is the Guillain–Barré syndrome. If there is absent sensory involvement, disorders such as polio, botulism, generalized myasthenia gravis, dyselectrlytemia, or acute myopathy can be considered. Some features are common for both hypokalemia and GBS but the hypokalemia is commonly ignored in the differential diagnosis. In acute myopathy, deep tendon reflexes are usually preserved and serum creatine phospo kinase levels are elevated. If paralysis develops acutely with prominent bladder retention, MRI of the spine should be done, to rule out a compressive meylopathy.

Electrophysiological studies are useful in confirming the site of lesion and confirming the primary pathology whether axonal versus demyelinating type. Early findings are seen in over 80% of GBS patients, and most will become abnormal with follow up studies. Frequent early abnormalities include prolonged F-wave latencies, absent H-reflexes, and the sural sparing effect on sensory studies. The

sural sparing effect is characterized by the pattern of a normal sural sensory study with abnormal upper limb sensory response. Patients with primary axonal pathology may have early decrement in compound muscle action potentials amplitudes. It is essential that multiple nerves be studied. The major features of primary demyelination which include prolonged distal latencies, reduced motor conduction velocities, prolonged F minimum latencies, and partial block in conduction with abnormal temporal dispersion).These findings typically evolve over the initial one to two weeks after disease onset. Recognition of these electro physiological features is essential in confirming a diagnosis of GBS and in differentiation between various subtypes of GBS. There are many electro physiological published criteria for acute inflammatory demyelinating polyneuropathy and chronic inflammatory demyelinating polyneuropathy. The physician should be aware that these criteria were mainly developed for research purposes, and not all AIDP patients will fulfill them.[33-36]

TABLE 1:DIAGNOSTIC CRITERIA FOR GBS

Features required for diagnosis	1. Progressive weakness in both arms and legs 2. Areflexia
Features strongly supporting diagnosis	1. Progression of symptoms over days, up to four weeks 2. Relative symmetry of symptoms 3. Mild sensory symptoms or signs 4. Cranial nerve involvement, especially bilateral weakness of facial muscles 5. Recovery beginning two to four weeks after progression ceases 6. Autonomic dysfunction 7. Absence of fever at onset 8. High concentration of protein in cerebrospinal fluid, with fewer than 10 cells per cubic millimeter 9. Typical electrodiagnostic features
Features excluding diagnosis	1. Diagnosis of botulism, myasthenia, poliomyelitis, or toxic neuropathy,abnormal porphyrin metabolism,recent diphtheria 2. Purely sensory syndrome, without weakness

PATHOGENESIS:

The exact pathogenesis of GBS is not yet well elucidated, but it is presumed as an organ specific immune mediated illness resulting from a synergistic interaction of humoral and cell mediated immune responses to peripheral nerve antigens. Each GBS subtype has a relatively independent immune pathogenesis.

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (AIDP):

Demyelination is the characteristic pathological feature of AIDP. The primary target for immune attack is mainly within the myelin. AIDP is characterized by the presence of predominant lymphocytic infiltration in the peripheral nerves associated with the invasion by macrophages in the myelin sheath and Schwann cells. Thus cellular immunity plays a critical role in the pathogenesis AIDP. This commonest form of Guillain-Barré syndrome is pathologically characterized by the presence of typical patchy segmental demyelination of the peripheral nerves resulting from macrophage invasion of the myelin sheath. Experimental allergic neuritis (EAN) was first demonstrated in 1955 by Waksman and Adams. This forms the basis as an animal model to investigate the mechanisms of AIDP. The major roles of T lymphocytes and macrophages have been shown by many studies including adoptive transfer

experimental allergic neuritis. These pathological features emphasize the predominant involvement of cellular immunity in the pathogenesis of AIDP.[57,58,59]

Autoreactive T-cells identify a specific auto antigen presented by MHC class II molecules. Activated T-lymphocytes cross the blood-nerve barrier and enter the peripheral nervous system causing activation of macrophages leading to the enhancement of macrophage mediated phagocytic activity resulting in the production of and the release of cytokines and other toxic mediators which ultimately result in the extension of demyelination and secondary axonal damage.

ACUTE MOTOR AXONAL NEUROPATHY:

This type of GBS is pathologically marked by axonal degeneration, which suggest the possible immune attack against the nerve axon. There may be reversible conduction block at the nodes of Ranvier. Among the precedent infections, C.jejuni is the commonest organism associated with AMAN. This type of GBS has been found to associated with various anti-ganglioside antibodies which include GM1, GM1b, GD1a or GalNAc-GD1a.[62,63] Many studies suggest that humoral immunity plays an important role in the pathogenesis of AMAN. "Molecular mimicry" plays an important role in the initiation of pathological events leading to AMAN. It was proved that some other preceding infectious organisms including EBV, CMV, Mycoplasma pneumoniae also have structural

similarity between their carbohydrate sequences (antigens) and with that of peripheral nerve tissues.[64,65,66]

This humoral immune response is characterized by the presence of auto antibodies which cross the blood-nerve barrier and causing axonal damage. This antibodies may be locally produced by B lymphocytes and causing direct axonal attack or through the activation of the complement system which ultimately result in resulting in predominant axonal damage with minimal demyelination. This axonal damage is histologically characterized by penetration of Schwann cell basal lamina by the macrophages thereby enter the periaxonal space,finally resulting in the axonal degeneration. This type of GBS is characterized by the absence of lymphocytic infiltration. Some studies demonstrated that even neuromuscular junction may play an important role as a site of antibody action.[62,63]

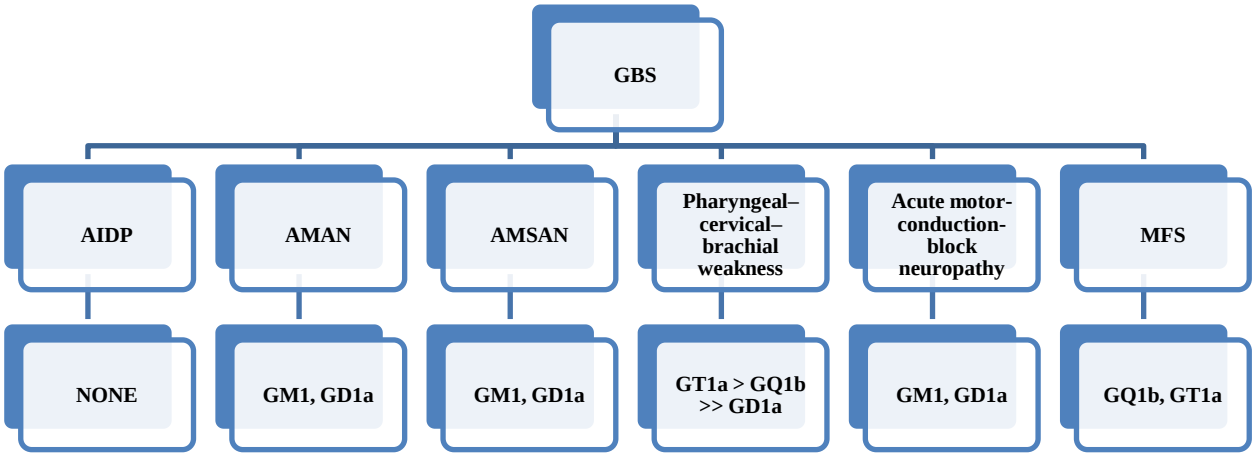
ACUTE MOTOR AND SENSORY AXONAL NEUROPATHY:

AMSAN is an another subtype of GBS with axonal pathology sharing many similar clinical and pathological features with AMAN except that the patients have major sensory involvement in addition to motor involvement. Studies have shown that some of anti-ganglioside antibodies (anti-GM1, anti-GM1b, and anti- GD1a IgG antibodies) are associated with this type of GBS.[21,67]

MILLER FISHER SYNDROME:

MFS is a rare variant of GBS characterized by the presence of elevated serum titers of Anti GQ1b and Anti GT1a antibodies which were consistently demonstrated in 90% and 100% of patients respectively. GQ1b is abundant in ocular muscle nerves, which may explain the vulnerability of the oculo motor system to immune mediated attack in these patients clinically characterized by the presence of ophthalmoplegia.[63]

DISORDERS OF GBS SPECTRUM WITH ASSOCIATED ANTIGANGLIOSIDE ANTIBODIES:



Khalili-Shirazi et al did a prospective study with the objective of demonstrating the association between anti ganglioside antibody seropositivity and Guillan-Barré syndrome after a recent cytomegalovirus infection. In their study Enzyme linked immunosorbant assay (ELISA) was done on serum samples from 14 patients with GBS with precedent cytomegalovirus infection and 12 without CMV infection, 17 patients with other neurological diseases, 11 patients with a recent CMV infection but without neurological involvement, 11 patients with recent Epstein-Barr virus infection but without neurological involvement, and 20 normal control subjects. They concluded that anti GM2 antibodies are commonly associated with GBS with precedent CMV infection, but their relevance in pathogenesis is not exactly known. In this study they found out that it is unlikely that CMV infection and anti GM2 antibodies are exclusively responsible for the pathogenesis and there may be an additional factor needed to elicit GBS.[68]

Koga et al did a retrospective study on 602 GBS patients. Out of these, 15 patients with bulbar involvement were included and serum antibodies against GM1, GM1b, GD1a, GalNAc- GD1a, GT1a, and GQ1b were examined in 13 of them. Serum anti ganglioside antibodies were found to be positive in eleven (85%) patients. IgG anti-GT1a was positive in eight patients (62%) and anti-GM1b was positive in seven patients (54%) .Anti GM 1 antibody was negative in all the

patients. Some patients had elevated anti- GD1a and anti-GQ1b antibody titres, but most had high GM1b or GT1a antibody titres. Antecedent diarrhoea was found in only one patient among the five patients with high IgG antibody titre to GM1b or GT1a. Anti GT1a antibody was found in some patients with pharyngeal-cervical brachial weakness .They also found that anti- GM1b and anti-GT1a antibodies were not associated with the presence of bulbar palsy. They observed complete recovery in sero negative patients. They concluded that the presence of serum IgG anti-GT1a and anti-GM1b antibodies support the diagnosis of GBS and its variants when there is early bulbar involvement.[69]

In a study conducted by Caudie et al the anti-ganglioside antibodies IgG and IgM were analyzed in 249 GBS cases by the immune dot blot technique. The anti-ganglioside autoantibodies are positive in 123 patients. In 62% of cases, precedent infection was found. The most frequently identified infectious agents are Campylobacter jejuni in 24% of cases and cytomegalovirus (CMV) in 7% of cases. Vaccination is found to be associated with 2% of GBS. Thirty eight percent of sero positive patients had severe illness requiring ventilator requirement. Anti ganglioside antibodies were absent in 126 patients or 50% of GBS. This study group demonstrated that anti ganglioside antibodies are helpful in the diagnosis of GBS with atypical picture and in different electro clinical variants of GBS. This technique immune dot blot is simple and cheap. The search for these

autoantibodies has become necessary in GBS assessment. The antiGD1a and antiGM1 were positive in axonal variant of GBS, antiGQ1b antibodies are always associated ophthalmoplegia and antiGD1b are always associated with GBS sensory ataxia.[70]

In a study conducted by Menon et al at National Institute of Mental Health and Neuroscience, Banglore, India twenty GBS patients were evaluated both clinically and electro physiologically and antiganglioside antibody profile were done in all these patients. Three types of antiganglioside antibodies were assessed namely GM1, GD1a and GD1b. Out of 12 sero positive patients , two had all the three antibodies positive. They found no significant correlation between clinical, electro physiological and immunological features of GBS.[71]

TREATMENT:

Before considering the treatment options in GBS it is essential to estimate the severity of GBS. There are various scales available for the functional grading of disability in GBS. Among them the most widely used clinical severity assessment scale is the Hughes functional grading scale which is depicted in table 2.[45] For motor power grading, MRC sum score is commonly used which is depicted in table 3. All these assessment scales are useful in monitoring the treatment response, disease progression and in research studies.

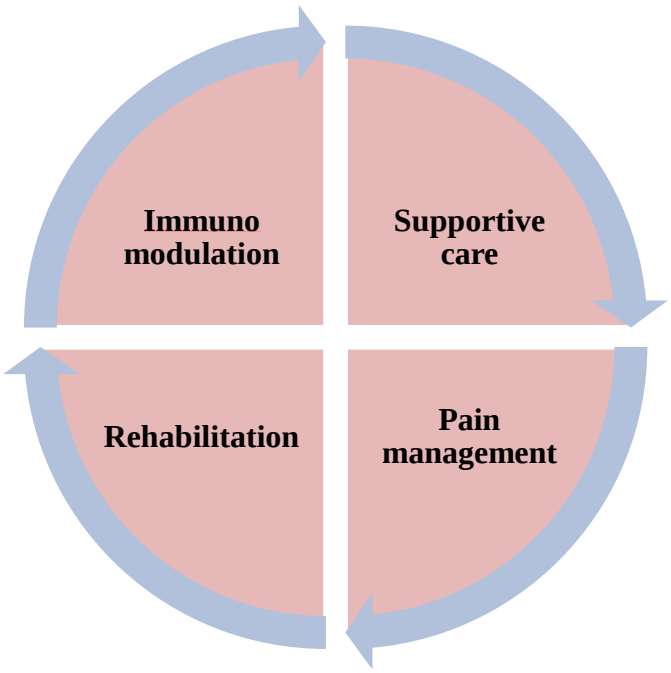
TABLE 2:HUGH`S FUNCTIONAL GRADING SCALE

SCORE	FEATURES
0	Healthy
1	Minor symptoms or signs, able to run
2	Able to walk 5 m independently
3	Able to walk 5 m with a walker or support
4	Bed- or chair-bound
5	Requiring assisted ventilation
6	Death

TABLE 3: MRC SUM SCORE

Parts	**Right (x/5)**	**Left(y/5)**	**Total(x+y)/10**
Upper arm abductors			
Elbow flexors			
Wrist extensors			
Hip flexors			
Knee extensors			
Foot dorsal flexors			
Total Score: Z/60 =			

TREATMENT SUB DIVISIONS IN GBS:



SUPPORTIVE TREATMENT:

Approximately one third of patients with severe GBS requires careful monitoring and requires mechanical ventilation. These patients must be carefully monitored in the intensive care setting particularly if there are autonomic sign, Hughes disability scale score ≥ 3 or <3 progressing. Intubation should be done if the patients show signs of bulbar dysfunction and aspiration.[62]

IMMUNOMODULATING TREATMENT:

Effective immunomodulating treatment has been shown to be effective in reducing nerve damage, slow progression, and shorten hospitalization. Plasma exchange and intra venous immune globulins are the effective available immunomodulatory treatment options at present. Both plasma exchange and IVIg

have been shown to exhibit beneficial effects in GBS by causing significant alteration in disease course. Their effectiveness is almost similar and both found to be superior than supportive treatment alone.

HIGH-DOSE IMMUNOGLOBULIN:

The empirical dose of IVIG commonly used for GBS treatment is 0.4 g/kg per day for five days. Six day course of IVIg has been shown to be superior in some studies but it was not statiscally significant. In pediatric GBS, IVIG has been demonstrated to cause significant speedy recovery of illness and has also been found to be safe and effective. Because of its superior efficacy, safety, and availability IVIG stands as the treatment of choice in many GBS patients.[72,73]

The mode of action of IVIG have not been fully elucidated, but it is known that IVIG has multiple actions including suppression of antibody production, acceleration of antibody removal, neutralization of complement-mediated damage, interference with antibody mediated cellular damage, modulation of nitric oxide synthesis and microglial function, direct action on T lymphocyte activation, cell adhesion inhibition, and initiation of apoptosis. Any or all of these may play a role in GBS treatment with IVIg.[74]

PLASMA EXCHANGE (PE):

Plasmaphresis is the first immune modulating therapy which was proved to be effective in GBS treatment. For mild GBS, Two exchanges are superior than none. For moderate and severe GBS four plasma exchanges are sufficient.If there is IVIg non responsiveness further plasma exchanges have not been found to be useful. The plasmaphresis regimen consists of exchange of approximately one plasma volume, 50 ml/kg. Many studies observed more side effects when fresh frozen plasma is used as the replacement fluid instead of albumin. Five percent albumin solution is routinely used as the replacement solution. If there is an increased risk of bleeding, fresh frozen plasma is beneficial than albumin.[75,76]

There are many modifications of plasma exchange have been tried to improve its safety and effectiveness like immunoadsorption and double filtration techniques. These modifications are mainly done to prevent the risk of infection and allergic events. CSF filtration has also been tried in some studies. None of these techniques were found to be superior to plasmaphresis in terms of safety and efficacy. Combined treatment of plasma exchange and IVIG is not found to be better than either alone.[77]

CORTICOSTEROIDS:

Corticosteroids are commonly used variety of autoimmune disorders. But GBS is an autoimmune disorder with exception to this treatment rule. Steroids

have not been found to be useful in GBS in many studies and is not recommended in GBS and some authorities even contra indicate its use in GBS.[40]

Pain is a major worrisome symptom observed in 89% of GBS patients; 75% of the GBS patients were found to be benefitted by oral or parenteral opioids and 30% were managed with intravenous infusion of morphine. 10 percent of the patients required tricyclic antidepressants and a further 10% received carbamazepine for neuropathic pain. Epidural infusion of morphine has been found to effective in the control of severe pain in GBS.[78]

Rehabilitation is essential for the speedy and effective recovery of GBS patients. Rehabilitation in the acute phase consists of gentle exercises which include isotonic, isometric, isokinetic exercises. During the disease course it should be focused on many measures such as proper limb positioning, nutrition, chest physiotherapy. On patients with significant disability orthotics should be used to prevent contractures.[78]

AIMS AND OBJECTIVES

1. To assess the anti ganglioside antibody profile in GBS and its variants
2. To assess the relevance of antibody profile in early diagnosis of GBS.
3. To evaluate the prognosis of GBS using the antibody profile.

MATERIALS AND METHODS

MATERIALS AND METHODS:

Acute phase serum (within 72 hours of onset of symptoms) was collected from patients (since May 2012) who got admitted in Rajivgandhi Government General Hospital and Madras Medical College with

(1) clinically defined syndrome comprising hyporeflexia, progressive symmetrical motor wakness and neurographic signs of motor and/or sensory peripheral neuropathy and

(2) no alternative or contributing causes of neuropathy (e.g.,diabetes mellitus, vitamin deficiency, vasculitis, electrolyte abnormalities, exposure to neurotoxins)

Detailed clinical and electrophysiological studies were done in all these patients. Using Euroline test kit by immuno blot method, IgG class of anti bodies against 7 gangliosides (GM1, GM2, GM3, GD1a, GD1b, GT1b &GQ1b) were tested in acute phase sera. The test kit contains test strips coated with parallel lines of purified antigens. The blot strips will be incubated in the first reaction step with diluted patient's serum. In case of positive samples, specific IgG antibodies will bind to the antigens coated in the strip. To detect the bound antibodies, a second incubation is done with enzyme labelled anti human IgG catalysing a colour reaction.

ETHICAL JUSTIFICATION:

A written informed consent was taken from the patient or caretakers after explaining the nature of study. The investigations planned were routinely indicated in the management of GBS. Three ml of blood was collected by venipuncture. The anti ganglioside antibody profile was done at free of cost. The information generated from this study helped in the appropriate management of cases.

STATISTICAL ANALYSIS:

Based on data from published literature, which reported prevalence of anti ganglioside antibody positivity in GBS, we conservatively assumed that around 60-70 % of our cohort would have seropositivity. To achieve ± 5% precision and 95% of confidence level, 40 sample size of GBS cases have been taken. For quantitative data, T test was applied. For qualitative test, chi square test was applied. For descriptive details, descriptive statistics was applied. Statistical analysis was conducted using SPSS 22.0 (SPSS, Chicago, IL, U.S.A).

RESULTS AND ANALYSIS

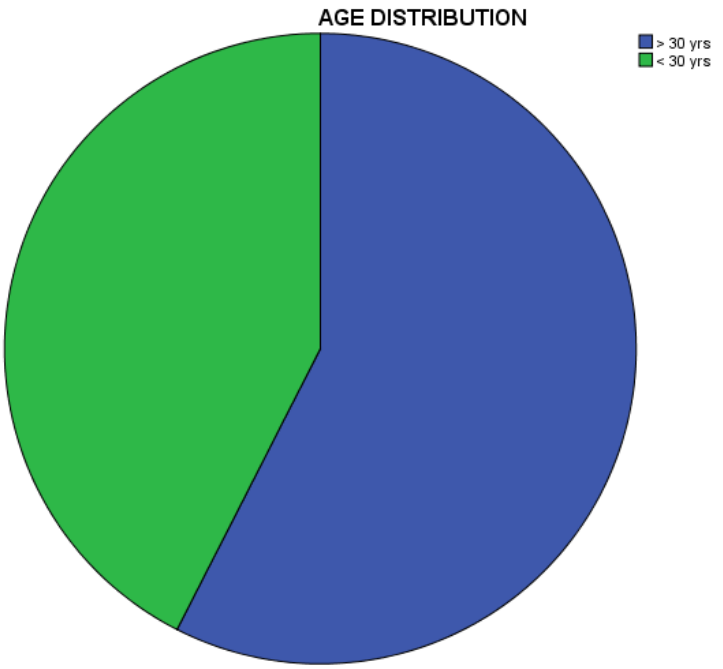
DEMOGRAPHIC PROFILE:

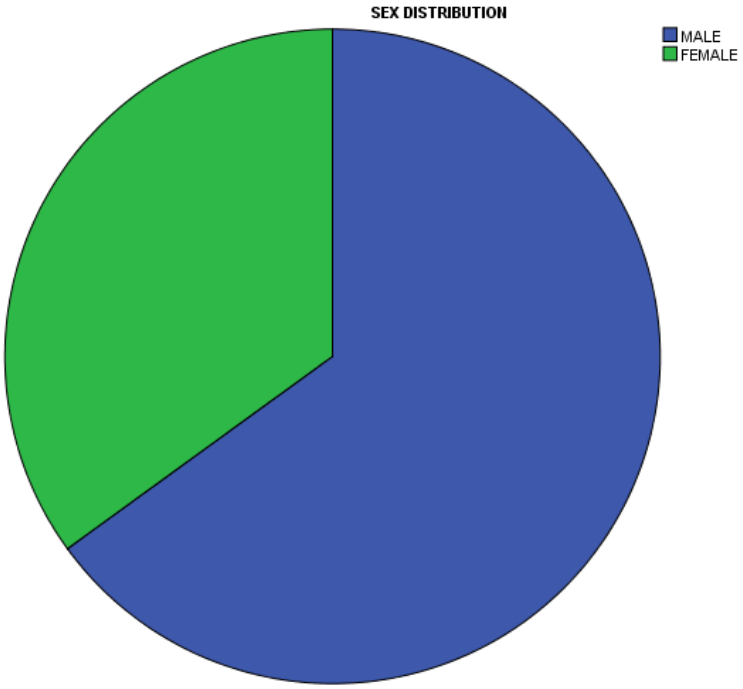
Out of 40 patients with GBS, 26 (65%) were male and 14(35%) were female.17 (42.5%) patients were in below 30 years age group and 23 (57.5%) were in above 30 years group. The mean age of our study cohort is 38.20 years with the standard deviation of 16.20 years. The median age of our study cohort is 36 years.The socio economic status of our study cohort is assessed by using the modified Kuppuswamy socio economic scale. The study cohort was classified into five socio economic classes on the basis of this scale. None of our study group belong to upper class. 4 (10%) patients belong to upper middle class, 14 (35%) patients belong to lower middle class, 13 (32.5%) patients belong to upper lower class and 9 (22.5 %) patients belong to lower class of socio economic scale. The mean socio economic status of our study cohort is 3.67 with the standard deviation of 0.94 . The median socio economic class of study group is 4 (UPPER LOWER).

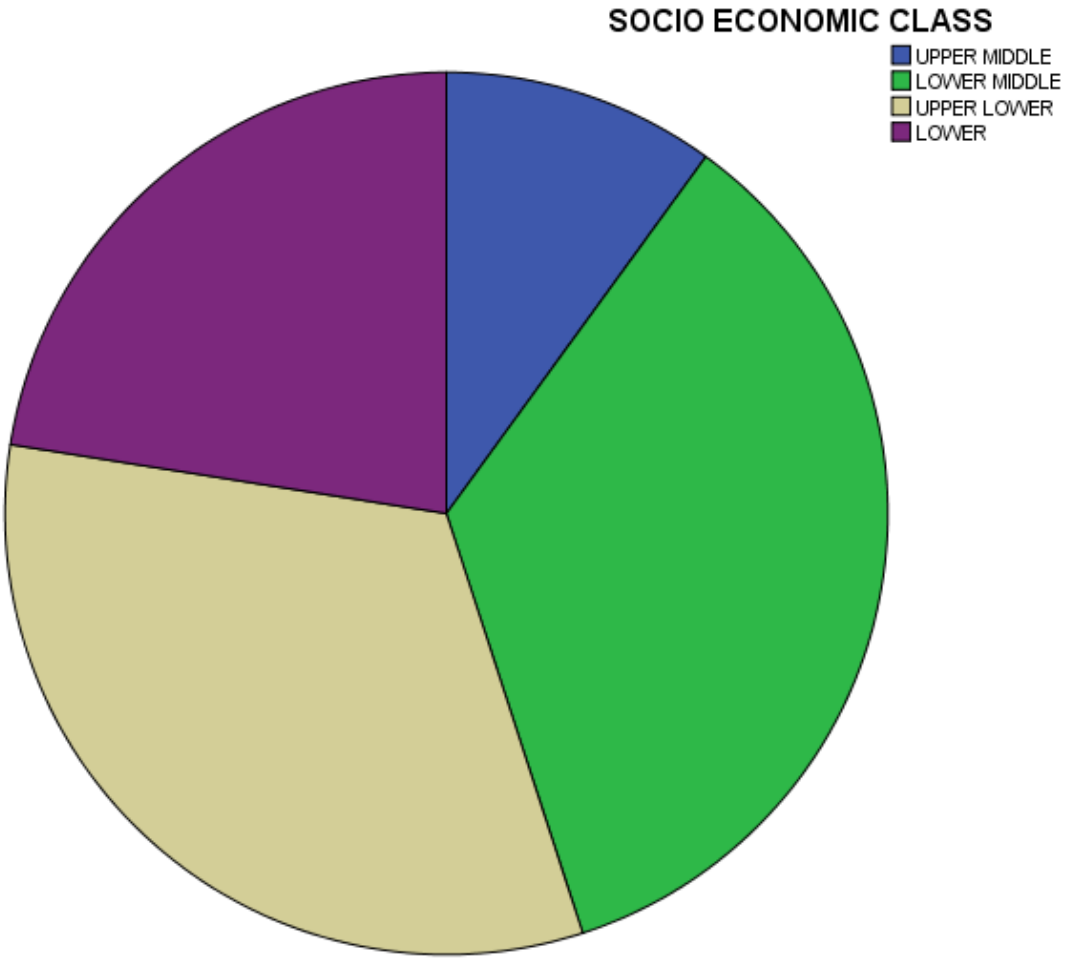
The demographic profile of our study group is depicted in Table 4.

TABLE 4: DEMOGRAPHIC PROFILE OF THE STUDY GROUP

VARIABLE	NUMBER	MEAN	MEDIAN	S.D
AGE AGE < 30 years AGE>30 years	N=40 17(42.5%) 23(57.5 %)	38.20	36.00	16.20
SEX MALE FEMALE	N=40 26(65%) 14(35%)	-	-	-
Socio Economic Status (Modified Kuppuswamy Scale)	I.UPPER - 0 (0%) II.UPPER MIDDLE -4 (10%) III.LOWER MIDDLE-14 (35%) IV.UPPER LOWER-13 (32.5 %) V.LOWER-9 (22.5%)	3.67	4.00	0.94


AGE DISTRIBUTION
> 30 yrs
< 30 yrs


SEX DISTRIBUTION
MALE
FEMALE


SOCIO ECONOMIC CLASS
UPPER MIDDLE
LOWER MIDDLE
UPPER LOWER
LOWER

CLINICAL PROFILE OF STUDY GROUP:

Out of 40 GBS patients, 14 (35%) patients had antecedent infection. Among these 14 patients, 7 (17.5%) had respiratory infection and the remaining 7 (17.5 %) had gastro intestinal infection. Sensory symptoms were present in 10 (25%) patients. Bulbar symptoms were present in 25 (62.5%) patients. Areflexia was present in all our patients. Ophthalmoplegia was present in 2 (5 %) patients. Autonomic signs were present in 12 (30 %) patients. The clinical features of our study group is depicted in table 5.

TABLE 5: CLINICAL PROFILE OF STUDY GROUP

VARIABLE	FREQUENCY	PERCENTAGE
Antecedent Infection	14	35
Respiratory Infection	7	17.5
Gastro Intestinal Infection (Diarrhea)	7	17.5
Sensory symptoms	10	25
Ophthalmoplegia	2	50
Areflexia	40	100
Bulbar Symptoms	25	62.5
Autonomic signs	12	30

ELECTRO PHYSIOLOGICAL PROFILE OF STUDY GROUP:

Out of 40 GBS patients, distal motor latencies were prolonged in 33 (82.5%) patients. Compound Motor Action Potential amplitude were reduced in 19 (47.5%) patients. Motor conduction velocities were decreased in 26 (65%) patients. F wave latency was prolonged in 36 (90 %) patients. On sensory conduction study, sensory nerve action potential amplitude was decreased in 15 (37.5%) patients. On the basis of clinical and electrophysiological analysis, our study group was divided into four GBS subtypes namely AIDP, AMAN, AMSAN and MFS. Out of 40 GBS patients, 15 (37.5 %) patients were AIDP, 13 (32.5 %) patients were AMAN, 10 (25 %) patients were AMSAN and 2 (5 %) patients were MFS.

The electrophysiological features of our study group is depicted in table 6.

TABLE 6: ELECTRO PHYSIOLOGICAL PROFILE OF STUDY GROUP

VARIABLE	FREQUENCY	PERCENTAGE
Prolonged DL	33	82.5
Reduced CMAP	19	47.5
Reduced CV	26	65
Prolonged F Latency	36	90
Reduced SNAP Amplitude	15	37.5

CLINICAL DISEASE SEVERITY PROFILE OF STUDY GROUP:

The disease severity of our study group was analyzed by using the following parameters namely time to peak illness (time taken for the illness to reach clinical nadir) in days, duration of illness in days, MRC sum score at admission and discharge, Hugh score at admission and discharge. The mean time taken for the illness to reach the nadir was 6.37 days with the standard deviation of 2.05 days. The median time to peak is 6 days. The mean duration of illness is 36.25 days with the standard deviation of 11.41 days. The mean MRC sum score at admission was 22.4 with the standard deviation of 13.58. The mean MRC sum score at discharge was 45.3 with the standard deviation of 6.13. The median MRC sum score at admission and discharge were 41 and 24 respectively. The mean Hugh score at admission was 4.42 with the standard deviation of 0.55. The mean Hugh score at discharge was 3.25 with the standard deviation of 0.49. The median Hugh score at admission and discharge was 4 and 3 respectively.

The clinical severity profile of our study group is depicted in table 7.

TABLE 7: CLINICAL DISEASE SEVERITY PROFILE OF STUDY GROUP

VARIABLE	MEAN	MEDIAN	S.D
Time to Peak (In days)	6.37	6.00	2.05
Duration of illness (In days)	36.25	41.00	11.41
Admission MRC score	22.4	24.00	13.58
Discharge MRC Score	45.3	46.00	6.13
Admission Hugh Score	4.42	4.00	0.55
Discharge Hugh Score	3.25	3.00	0.49

IMMUNOLOGICAL PROFILE IN GBS SUBTYPES:

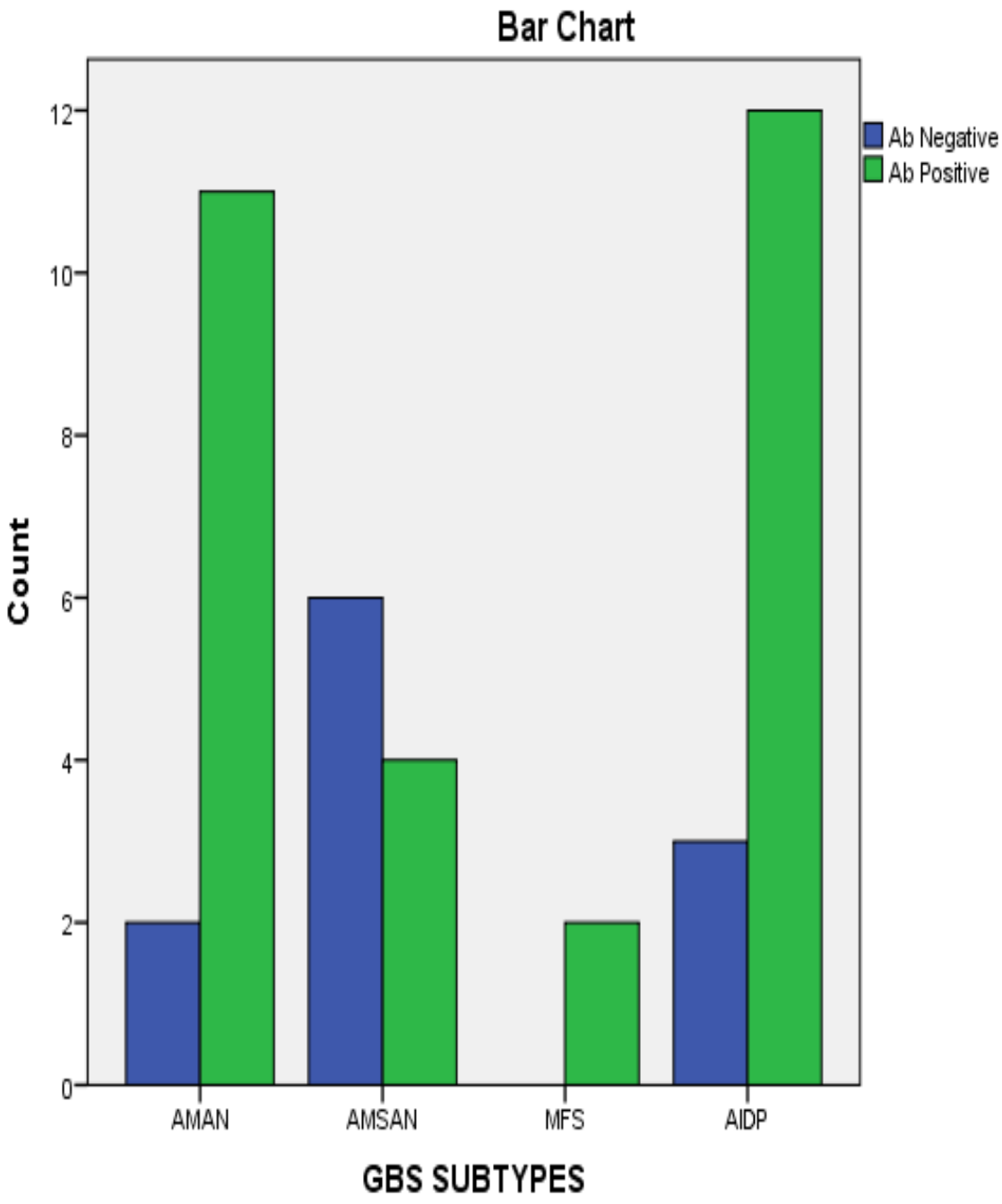
Out of 40 patients with GBS 29 (72.5%) patients showed anti ganglioside antibody positivity. Among 15 patients with AIDP, 12 (80%) patients were seropositive. Among 13 patients with AMAN, 11 (85%) were seropositive. Among 10 patients with AMSAN, 4 (10%) patients were seropositive. Among 2 MFS patients both (100 %) were seropositive.

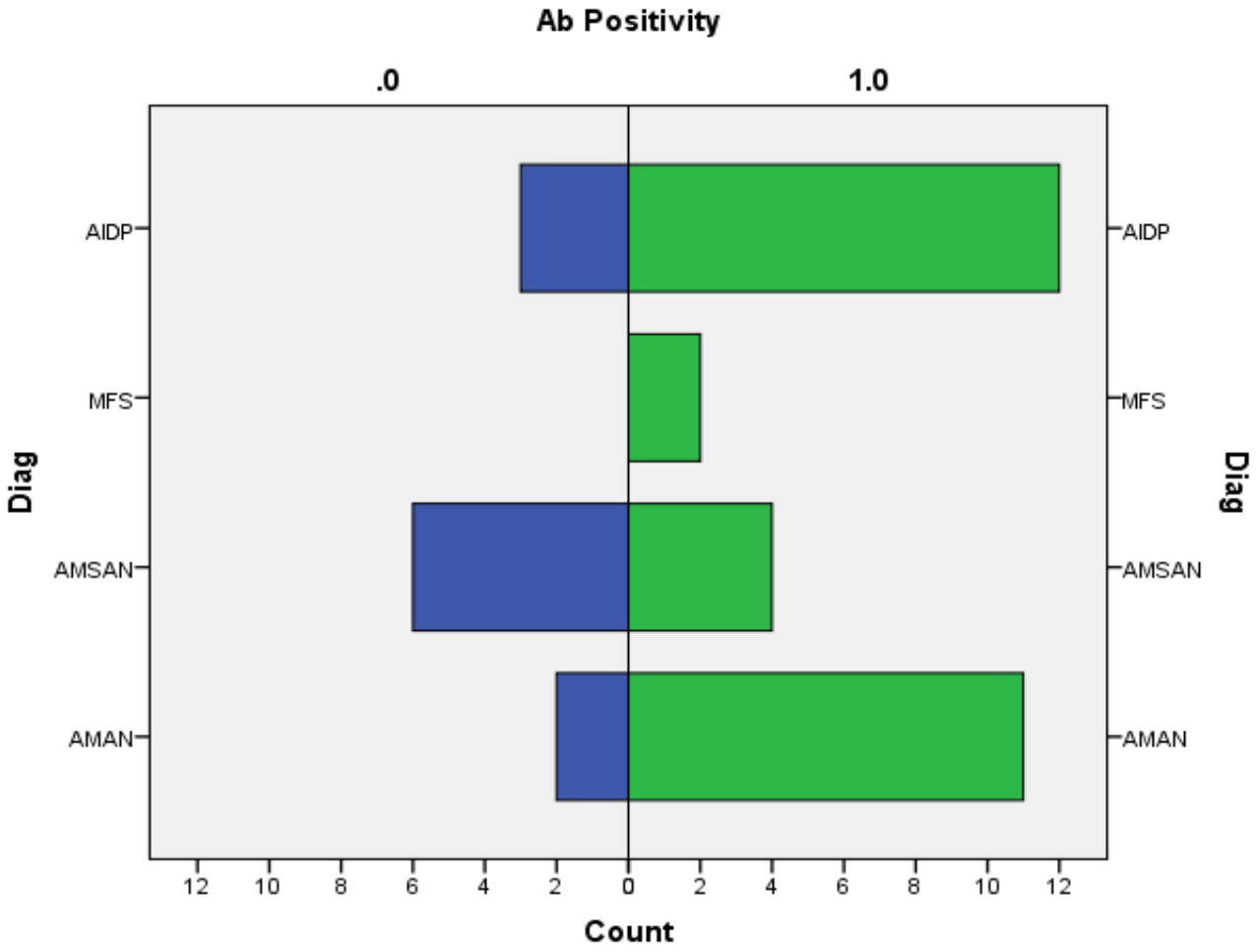
Anti GM1 ganglioside antibody was positive in 14 patients of GBS which include 6 AIDP patients, 7 AMAN patients and one AMSAN patient. Anti GM2 ganglioside antibody was positive in 19 patients of GBS which include 10 AIDP patients, 7 AMAN patients and 2 AMSAN patients. Anti GM3 ganglioside antibody was positive in 12 patients of GBS which include 5 AIDP patients, 5 AMAN patients and 2 AMSAN patients. Anti GD1a ganglioside antibody was positive in 6 patients of GBS which include 4 AIDP patients, one AMAN patient and one AMSAN patient. Anti GD1b ganglioside antibody was positive in 2 patients of GBS which include one AIDP patient and one AMSAN patient. Anti GT1b ganglioside antibody was positive in one GBS patient which is a case of AMAN. Anti GQ1b antibody was positive in 2 GBS patients who were MFS.

The immunological profile of our study group is depicted in table 8.

TABLE 8: IMMUNOLOGICAL PROFILE IN GBS SUBTYPES

GBS TYPE	Antiganglioside Antibody positivity	GM1	GM2	GM3	GD1a	GD1b	GT1b	GQ1b
AIDP	12(15) (80 %)	6	10	5	4	1	0	0
AMAN	11(13) (85%)	7	7	5	1	1	1	0
AMSAN	4(10) (40%)	1	2	2	1	0	0	0
MFS	2(2) (100 %)	0	0	0	0	0	0	2
TOTAL	29(40) (72.5%)	14	19	12	6	2	1	2


Bar Chart
Ab Negative
Ab Positive
Count
0
2
4
6
8
10
12
AMAN
AMSAN
MFS
AIDP
GBS SUBTYPES


Ab Positivity
.0
1.0
AIDP
MFS
AMSAN
AMAN
Diag
Diag
12
10
8
6
4
2
0
2
4
6
8
10
12
Count

TREATMENT DETAILS IN STUDY GROUP:

Among 40 GBS patients, 22 (55%) patients required ventilator support. Twenty eight patients (70%) received intra venous immunoglobulin. Plasma exchange was done in 17 (42.5%) patients.

The treatment details of our study group is depicted in table 9.

TABLE 9: TREATMENT DETAILS IN STUDY GROUP

TREATMENT	NUMBER	PERCENTAGE
Ventilation	22	55
IvIg	28	70
Plasmaphresis	17	42.5

CLINICAL CORRELATION OF IMMUNOLOGICAL PROFILE:

With regard to age, anti ganglioside antibodies were positive in 12 patients of below 30 years age group and in 17 patients of above 30 years age group. These ganglioside antibodies were negative in 5 patients of below 30 years age group and in 6 patients of above 30 years age group. There is statistically significant higher antiganglioside antibody positivity in above 30 years age group.

With regard to sex, antiganglioside antibodies were positive in 19 males and in 10 females. These antiganglioside antibodies were negative in 7 males and in 4 females. There is statistically significant higher antibody positivity in males.

With regard to antecedent infection, antiganglioside antibodies were positive in 12 patients and negative only in 2 patients. There is statistically significant higher antibody positivity in patients with antecedent infections.

With regard to bulbar symptoms, anti ganglioside antibodies were positive in all 25 patients with bulbar symptoms. There is statistically significant anti ganglioside antibody positivity in GBS patients with bulbar symptoms.

With regard to autonomic signs, anti ganglioside antibodies were positive in all 12 patients with autonomic signs. There is statistically significant higher antibody positivity in GBS with autonomic signs.The clinical correlation of immunological profile is depicted in table 10.

TABLE 10: CLINICAL CORRELATION OF IMMUNOLOGICAL PROFILE

VARIABLE	ANTIBODY POSITIVE	ANTIBODY NEGATIVE	SIGNIFICANCE (P Value)
AGE			
AGE <30 yrs	12	5	0.05
AGE >30 yrs	17	6	
SEX			
MALE	19	7	0.01
FEMALE	10	4	
ANTECEDENT INFECTION			
YES	12	2	0.01
NO	17	9	
BULBAR SYMPTOMS			
YES	25	0	0.01
NO	4	11	

AUTONOMIC SIGNS			
YES	12	0	0.01
NO	17	11	

CLINICAL SEVERITY CORREALTION WITH IMMNOLOGICAL PROFILE:

Among the 29 sero positive patients, 27 patients reached the peak of illness in less than one weak duration whereas only 2 seronegative patients reached the nadir in less than one weak. There is statistically significant higher antibody positivity in patients who reach the clinical nadir in less than one weak.

Among the 29 sero positive patients, 28 had the duration of illness lasted for more than one month and only one patient recovered within one month period. There is statistically significant higher antibody positivity in patients with longer duration (more than a month) of illness.

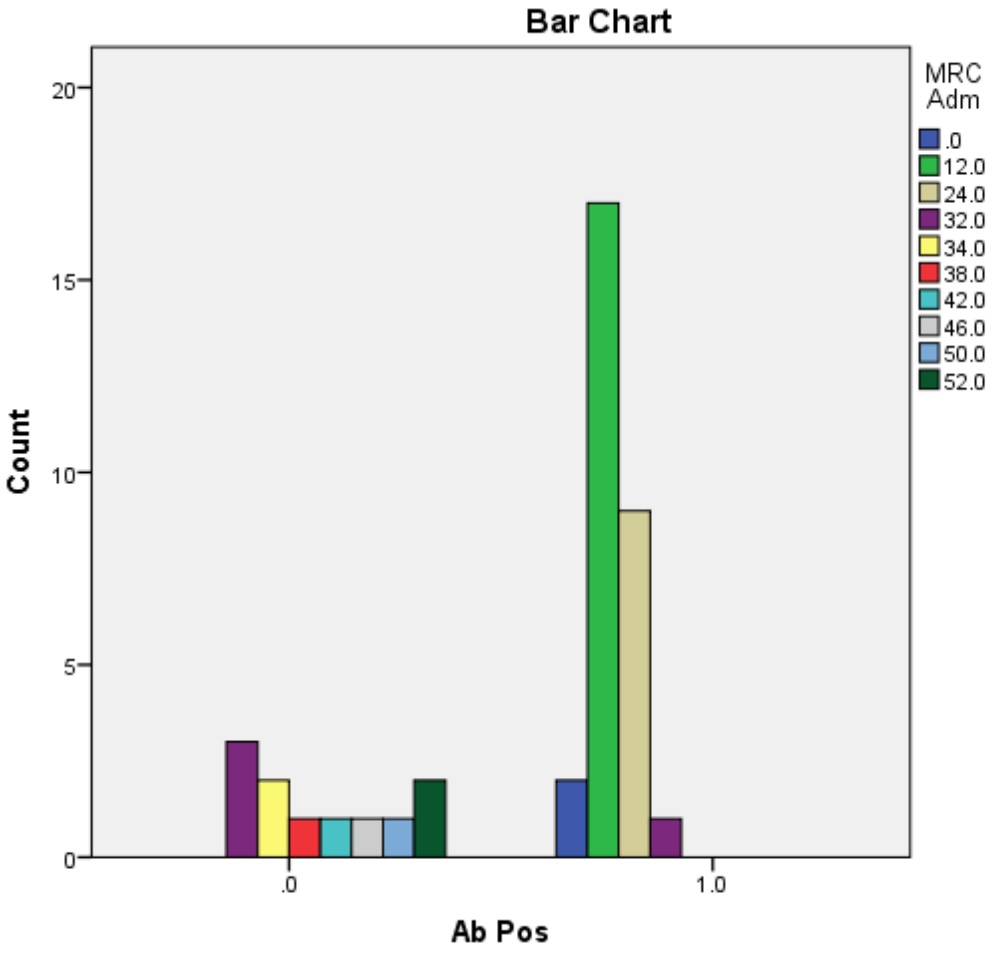
Among the 29 sero positive patients, 21 patients required ventilator support, whereas 8 patients did not require ventilator support. There is statistically significant higher antibody positivity in GBS patients who require ventilator support.

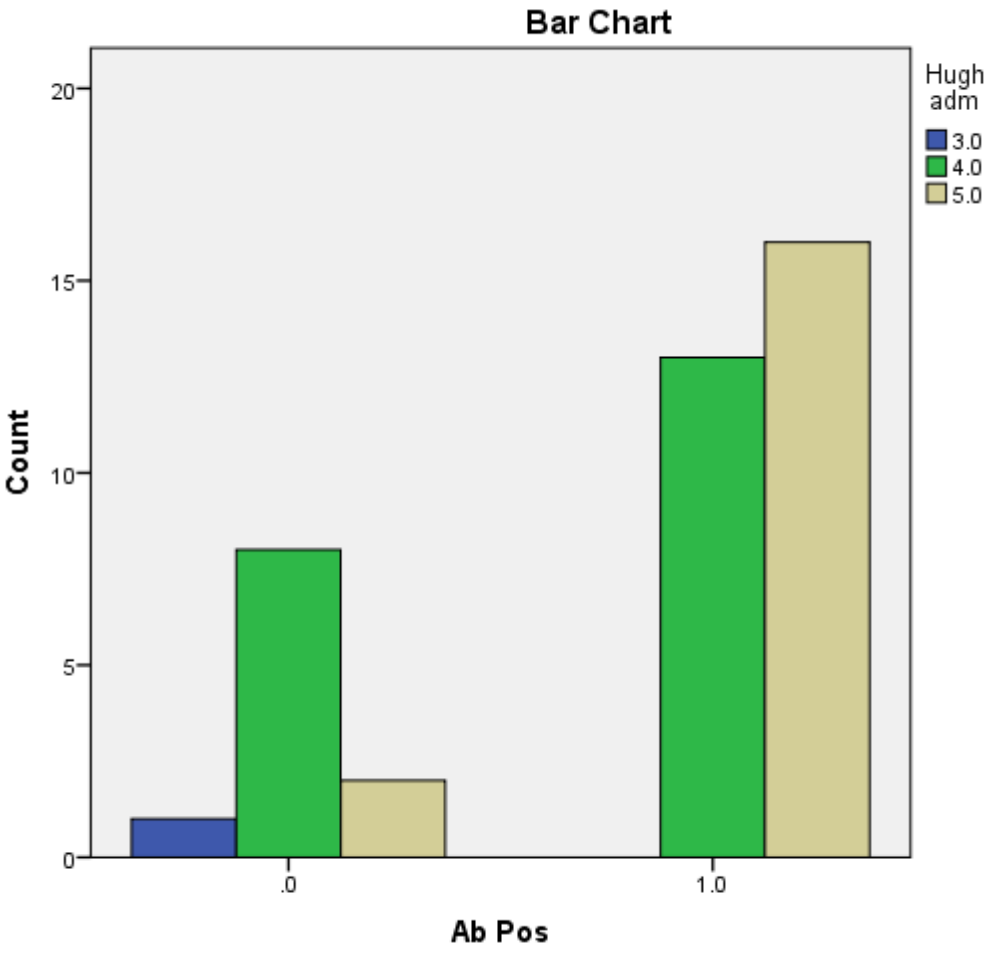
Among the 29 sero positive patients, 28 patients had MRC sum score of less than 30 at admission where as only one patient had the score of more than 30.There is statistically significant higher antibody positivity in patients with low MRC sum score (less than 30) at admission.

The correlation between the clinical and immunological profile of our study group is depicted in table 11.

TABLE 11: CLINICAL SEVERITY CORREALTION WITH IMMNOLOGICAL PROFILE

VARIABLE	ANTIBODY POSITIVE	ANTIBODY NEGATIVE	SIGNIFICANCE
TIME TO PEAK			
< 7 days	27	2	0.01
>7 days	2	9	
DURATION OF ILLNESS			
<4 weeks	1	10	0.01
>4 weeks	28	1	
VENTILATION			
YES	21	1	0.01
NO	8	10	
ADMISSION MRC SUMSCORE			
<30	28	0	0.01
>30	1	11	


Bar Chart
MRC Adm
.0
12.0
24.0
32.0
34.0
38.0
42.0
46.0
50.0
52.0
Count
20
15
10
5
0
.0
1.0
Ab Pos


Bar Chart
Hugh adm
3.0
4.0
5.0
Count
20
15
10
5
0
.0
1.0
Ab Pos

DISCUSSION

Pervious documented studies has demonstrated that at least half of GBS patients showed anti ganglioside antibody positivity during the acute phase of illness.[70] Our study showed 72.5 % antibody positivity in the acute phase of illness. This finding correlates well with the previous research reports. Among the techniques used in antibody analysis, none is found superior to other. In our study ELISA was used as in many previous studies. This high antibody positivity in our cohort can be explained by two things. First it has been proved that antiganglioside antibody positivity is more common in GBS with preceding infections. In our study 14 patients had the history of precedent infection. In our part of country respiratory and gastro intestinal infections are common because of poor hygiene and sanitation. This may account for the higher sero positive rates in our study group. Secondly, many studies found an association between the severity of illness and antiganglioside antibody positivity.[70,71] Though, our cohort has a mixture of population with variable disease severity, severe illness was found in many patients. This higher percentage of very severe illness group might have contributed this high degree of sero positivity in our study group.

Our study has shown significant sero positivity in patients with antecedent infections. This has been very well demonstrated in many of the previous studies.[68,69] This could be explained by the presumed pathogenic role of

molecular mimicry between the micro organisms and the gangliosides of peripheral nervous tissue. Our cohort had equal percentage of respiratory and gastro intestinal infections preceding GBS. The most common infections reported to be associated with GBS in adults are gastrointestinal (6–26%) and respiratory (22–53%) infections. Antecedent infections are usually more common in children (67–85%) with a larger frequency of respiratory (50–70%) than gastrointestinal (7–14%). The most common organism found to be associated with GBS is campylobacter jejuni.[46-49] In our study search for micro organisms could not be done because of limited resources.

Previous studies have shown strong positive correlation between the disease severity and anti ganglioside antibody positivity.[68-71] Our study also demonstrated the similar phenomenon. In our study among the 29 sero positive patients, 27 patients reached the peak of illness in less than one weak duration whereas only 2 seronegative patients reached the nadir in less than one weak. There is statistically significant higher antibody positivity in patients who reach the clinical nadir in less than one weak. Now it has been clear that sero positive patients usually follow a severe course of illness with rapid onset peak illness. The MRC sumscore of our antibody positive group was significantly lower than that of sero negative group. This could be due to severe motor impairment in sero positive group when compared to less severe motor involvement in sero neagative group.

Our study has shown significantly higher antibody positivity in patients with bulbar and autonomic involvement.[69] This finding has been documented in many previous studies. Our cohort had two patients with Miller Fisher syndrome. Both of them showed anti GQ1b antibody positivity. Anti-GQ1b IgG antibodies are found to be highly sensitive and specific of MFS. It has also been found in some patients with AIDP with acute ophthalmoplegia. Some researchers suggest that anti- GQ1b IgG antibodies may play a significant role in the development of typical clinical signs seen in MFS.

Most of our antibody positive patients required mechanical ventilation as a result of severe illness. The sero positive group took longer than usual time for recovery when compared to sero negative patients. The Hugh score has been used as a disability assessment score in our study like in many previous studies. This score was significantly high with the sero positive patients. There was no significant improvement in the muscle power and Hugh score was observed in antibody positive group.

This study extends the previous findings on the relationship between antiganglioside antibodies and GBS. Though many studies on this topic are available from western countries, very few have been done in our country. Among the available studies , number of patients included in the study was low with occasional case reports of sero positivity. To overcome these limitations, this study

was done to assess the anti ganglioside antibody positivity in GBS patients and its correlation with disease severity.

CONCLUSIONS

1. Assessment of antiganglioside antibody profile in GBS helps in the detection of disease in the early phase of illness.
2. Antiganglioside antibodies are useful in prognostication of GBS.
3. Antiganglioside antibodies are invariably present in severe GBS.
4. Larger sample size is required to make any definite meaningful correlation and utility of these antiganglioside antibodies in GBS.

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ANNEXURES

ANNEXURE I

ABBREVIATIONS

AIDP- Acute Inflammatory Demyelinating Polyradiculoneuropathy

AMAN- Acute Motor Axonal Neuropathy

AMSAN- Acute Motor Sensory Axonal Neuropathy

CMAP- Compound Muscle Action Potential

GBS- Guillain Barre Syndrome

IVIg- Intravenous Immunoglobulin

MFS- Miller Fisher Syndrome

NCS- Nerve Conduction Study

PE- Plasma Exchange

SNAP- Sensory Nerve Action Potential

ANNEXURE II
PATIENT CONSENT FORM

Study Details: Anti Ganglioside Antibody profile in GBS - Clinical Immunological And Neurophysiological Significance
Study Centre: Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai - 600 003.

Patient may check (□) these boxes:

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical (Serum CK) radiological, EMG, NCS and muscle biopsy, appropriate to the clinical diagnosis. ☐

I hereby consent to participate in this study. ☐

Signature / Thumb impression:

Patient Name and Address: Place : Date :

Signature of Investigator

Study Investigator's Name : Place : Date :

ANNEXURE III

INFORMATION SHEET

- We are conducting a study of the **"Anti Ganglioside Antibody profile in GBS - Clinical , Immunological And Neurophysiological Significance"** at Institute of neurology**,** Rajiv Gandhi Government General Hospital, Chennai. The purpose of this study is to to investigate the prognostic value of the antiganglioside antibodies in GBS
- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator ***Signature of Participant***

Date:

ANNEXURE IV

CASE PROFORMA

ANTI GANGLIOSIDE ANTIBODY PROFILE IN GBS - CLINICAL, IMMUNOLOGICAL AND NEUROPHYSIOLOGICAL SIGNIFICANCE – CASE PROFORMA

Name:

Age/Sex:

Address:

Phone Number:

Education:

Occupation:

Socio Economic Class (Modified Kuppuswamy Scale):

I.UPPER

II.UPPER MIDDLE

III.LOWER MIDDLE

IV.UPPER LOWER

V.LOWER

CLINICAL DETAILS

1.Chief Complaints:

2.Duration of symptoms (in days):

3.Antecedent illness:

1.Yes

2.No

4.If Yes,

1.Gastrointestinal

2.Respiratory

3.Others

5. Interval between antecedent illness and onset of symptoms (in days):

6. Associated Illness :

a.DM : Yes / No

b.SHT : Yes / No

c.Alcoholism : Yes / No

d.Smoking : Yes / No

e.Hypothyroidism : Yes / No

7. Vital Signs :

PR : Single Breath Count :

BP : Spo2 :

8. Neurological Examination :

HMF :

Cranial Nerve Examination :

Spino Muscular System :

	Rt UL	Rt LL	Lt UL	Lt LL
Bulk				
Tone				
Power				

MRC SUM SCORE :

Parts	Right (x/5)	Left(y/5)	Total(x+y)/10
Upper arm abductors			
Elbow flexors			
Wrist extensors			
Hip flexors			
Knee extensors			
Foot dorsal flexors			
Total Score: Z/60 =			

Reflexes :

	BJ	TJ	SJ	KJ	AJ	Plantar
Rt						
Lt						

Sensory System :

Autonomic Nervous System :

The modified *Hughes functional grading scale* (f score):

SCORE	FEATURES
0	Healthy
1	Minor symptoms or signs, able to run
2	Able to walk 5 m independently
3	Able to walk 5 m with a walker or support
4	Bed- or chair-bound
5	Requiring assisted ventilation
6	Death

Scale at admission:

Scale at nadir:

Scale at discharge:

Treatment Received :

IvIg :

Plasmapheresis :

Mechanical Ventilation Duration :

Others :

Ganglioside Antibody Profile :

Ab	Intensity	Result
GM1		
GM2		
GM3		
GD1a		
GD1b		
GT1b		
GQ1b		

Nerve Conduction Study :

CMAP	Lat	Amp	CV	F lat
Rt Median				
Lt Median				
Rt Ulnar				
Lt Ulnar				
Rt Tibial				
Lt Tibial				
Rt Peroneal				
Lt Peroneal				

SNAP	Lat	Amp	CV
Rt Median			
Lt Median			
Rt Ulnar			
Lt Ulnar			
Rt Sural			
Lt Sural			

Interpretation:

Motor:

	Median	Ulnar	Common Peroneal
Prolonged DL			
Reduced CMAP amp			
Reduced NCV			
Absent or Prolonged F wave latency			
Inexcitable nerve			

Sensory:

	Median	Ulnar	Sural
Absent SNAP			
Reduced SNAP amp			
Reduced NCV			

FINAL DIAGNOSIS :

1.AMAN

2.AMSAN

3.MFS

4.AIDP

5.MFS plus

6.Other types

ANNEXURE V

MASTER CHART

Name	Age	AGE DISTRIBUTION	Age>30	SEX	MK Scale	Ant Inf	Type of Inf	Pre dur	Bulbar	Auto	Ophthal	sensory
Arukutty	54	0	1	1	2	0	0	0	0	0	0	0
Balagurusamy	64	0	1	1	3	1	2	10	1	0	1	0
Banumathi	51	0	1	2	2	1	2	14	0	0	0	1
Ganesan	35	0	1	1	3	0	0	0	1	0	1	0
Gunasekar	51	0	1	1	4	0	0	0	0	1	0	0
Rani	55	0	1	2	3	0	0	0	0	1	0	0
Sundar Raj	57	0	1	1	2	0	0	0	1	0	0	0
Natarajan	48	0	1	1	3	0	0	0	0	0	0	0
Nagammal	60	0	1	2	2	0	0	0	1	1	0	0
Yuvaraj	30	1	0	1	3	1	2	10	1	1	0	0
Suganya	20	1	0	2	4	1	1	10	1	0	0	0
Annamalai	48	0	1	1	3	0	0	0	0	0	0	1
Mukesh	37	0	1	1	3	0	0	0	1	0	0	0
Nandhini	17	1	0	2	4	1	1	10	0	0	0	1
Navaneetham	67	0	1	2	3	0	0	0	1	1	0	0
Palraj	35	0	1	1	4	0	0	0	1	0	0	0
Perumal	26	1	0	1	3	0	0	0	0	0	0	1
Prakash	23	1	0	1	4	1	2	12	1	1	0	1
Radhika	20	1	0	2	3	1	1	10	1	0	0	0
Sigamani	45	0	1	1	4	0	0	0	1	1	0	1
Rahman	28	1	0	1	3	1	1	12	1	0	0	0
Satheesh	15	1	0	1	3	1	1	10	1	1	0	0
Sathyaraj	25	1	0	1	4	1	1	10	1	0	0	1
Sudhakar	20	1	0	1	4	0	0	0	0	0	0	0

Name	Age	AGE DISTRIBUTION	Age>30	SEX	MK Scale	Ant Inf	Type of Inf	Pre dur	Bulbar	Auto	Ophthal	sensory
Suran raj	23	1	0	1	3	0	0	0	0	0	0	1
Rajesh	17	1	0	1	4	1	1	10	1	1	0	1
Sivaprakash	31	0	1	1	3	0	0	0	1	0	0	0
Remosh khan	20	1	0	1	4	0	0	0	0	0	0	0
Prema	55	0	1	2	5	1	2	10	1	0	0	0
Neelakandan	30	1	0	1	4	0	0	0	0	0	0	1
Nagenramma	43	0	1	2	5	0	0	0	0	0	0	0
Amala	18	1	0	2	5	0	0	0	1	1	0	0
Ashok kumar	55	0	1	1	4	0	0	0	1	1	0	0
Karthik	37	0	1	1	5	0	0	0	0	0	0	0
Nakammal	55	0	1	2	5	1	2	10	1	1	0	0
Tamilarasi	56	0	1	2	5	1	2	12	1	0	0	0
Kottishwari	24	1	0	2	4	0	0	0	0	0	0	0
Vijayalaxmi	69	0	1	2	5	0	0	0	1	0	0	0
Bosa durai	40	0	1	1	5	0	0	0	1	0	0	0
Thilagan	24	1	0	1	5	0	0	0	1	0	0	0

Dur Peek	Dur PK <7	Venti	IvIg	PP	Recov	Recov4 wk	MRC Adm	MRCAd< 30	MRC Ds	Hugh adm	Hugh Ds	Pro DL	Red CMAP	Red CV	Pro F	Inex Ner
14	0	0	0	0	22	1	50	0	56	3	2	1	0	1	1	0
4	1	1	1	0	42	0	0	1	48	4	3	1	1	0	1	0
8	0	0	1	0	14	1	32	0	48	4	3	1	1	1	1	0
5	1	1	0	1	42	0	12	1	48	5	3	1	1	1	1	0
4	1	1	1	1	44	0	0	1	48	5	3	0	0	0	1	1
4	1	1	0	1	42	0	12	1	48	5	3	1	0	1	1	0
4	1	1	0	1	48	0	12	1	48	5	3	0	0	0	0	1
8	0	0	1	0	21	1	34	0	48	4	3	1	1	1	1	0
4	1	1	1	0	40	0	12	1	42	5	4	1	0	0	1	0
7	1	1	1	1	42	0	12	1	40	5	4	1	0	1	1	0
6	1	1	1	0	48	0	12	1	44	5	3	1	1	1	1	0
8	0	0	0	1	24	1	46	0	52	4	3	1	1	0	1	0
6	1	0	0	1	42	0	24	1	48	4	3	1	1	1	1	0
8	0	1	1	1	52	0	52	0	32	5	4	0	0	0	0	1
7	1	1	1	0	56	0	12	1	48	5	4	1	0	1	1	0
4	1	0	1	0	42	0	24	1	52	4	3	1	1	1	1	0
8	0	0	0	0	21	1	52	0	46	4	3	1	1	0	1	0
6	1	1	1	1	44	0	12	1	42	5	4	0	0	0	1	1
4	1	0	0	1	42	0	24	1	42	4	3	1	0	1	1	0
6	1	1	1	1	62	0	12	1	32	5	4	0	0	0	1	1
7	1	0	0	1	32	0	24	1	44	4	3	1	1	1	1	0
7	1	1	1	0	32	0	24	1	42	4	3	1	0	1	1	0
6	1	1	1	1	54	0	12	1	34	5	4	0	0	0	0	1
8	0	1	0	1	24	1	12	1	46	4	3	1	1	0	1	0
6	1	0	1	0	21	1	32	0	44	4	3	1	1	1	1	0
5	1	1	1	1	42	0	24	1	42	5	4	0	0	0	0	1
7	1	0	1	0	34	0	12	1	54	4	3	1	0	1	1	0
8	0	0	1	0	32	0	24	1	52	4	3	1	0	1	1	0

Dur Peek	Dur PK <7	Venti	IvIg	PP	Recov	Recov4 wk	MRC Adm	MRCAd< 30	MRC Ds	Hugh adm	Hugh Ds	Pro DL	Red CMAP	Red CV	Pro F	Inex Ner
6	1	1	1	0	42	0	12	1	42	5	3	1	0	1	1	0
8	0	0	1	0	21	1	32	0	44	5	3	1	1	1	1	0
10	0	0	1	0	22	1	42	0	48	4	3	1	0	0	1	0
6	1	1	1	0	35	0	12	1	52	4	3	1	1	1	1	0
4	1	1	0	1	32	0	24	1	52	4	3	1	1	0	1	0
6	1	0	1	0	24	1	34	0	46	4	3	1	1	1	1	0
6	1	1	1	0	42	0	32	0	42	5	4	1	1	1	1	0
4	1	1	1	0	44	0	12	1	34	5	4	1	0	1	1	0
9	0	0	1	0	21	1	38	0	42	4	3	1	0	1	1	0
7	1	0	0	1	32	0	12	1	54	4	3	1	0	1	1	0
4	1	1	1	0	42	0	12	1	34	5	4	1	1	1	1	0
6	1	0	1	0	32	0	24	1	52	4	3	1	1	1	1	0

Abs SNAP	Red SNAP	Red CV	GM1	GM2	GM3	GD1a	GD1b	GT1b	GQ1b	Diag	Ab Pos
1	1	1	0	0	0	0	0	0	0	4	0
0	0	0	0	0	0	0	0	0	1	3	1
0	0	0	0	0	0	0	0	0	0	2	0
0	0	0	0	0	0	0	0	0	1	3	1
0	0	0	1	0	0	0	0	0	0	1	1
1	1	1	1	1	0	0	0	0	0	4	1
0	0	0	1	1	0	0	0	0	0	1	1
0	0	0	0	0	0	0	0	0	0	1	0
1	1	1	0	0	0	1	0	0	0	4	1
1	1	1	0	1	1	1	1	0	0	4	1
0	0	0	0	0	1	0	0	0	0	1	1
1	1	1	0	0	0	0	0	0	0	2	0
0	0	0	1	1	1	0	0	0	0	1	1
0	0	0	0	0	0	0	0	0	0	2	0
1	1	1	1	1	0	0	0	0	0	4	1
0	0	0	1	1	0	0	0	0	0	1	1
1	1	1	0	0	0	0	0	0	0	2	0
0	0	0	1	1	0	0	0	0	0	2	1
0	0	0	1	1	0	0	0	0	0	4	1
0	0	0	0	0	0	1	0	0	0	2	1
0	0	0	1	1	0	0	0	0	0	1	1
0	0	0	1	1	0	0	0	0	0	4	1
0	0	0	0	1	1	0	0	0	0	2	1
0	0	0	1	1	0	0	0	0	0	1	1
1	1	1	0	0	0	0	0	0	0	2	0
0	0	0	0	0	1	0	0	0	0	2	1

Abs SNAP	Red SNAP	Red CV	GM1	GM2	GM3	GD1a	GD1b	GT1b	GQ1b	Diag	Ab Pos
1	1	1	1	1	0	0	0	0	0	4	1
0	0	0	1	1	0	0	0	0	0	4	1
0	0	0	0	1	1	0	0	0	0	4	1
1	1	1	0	0	0	0	0	0	0	2	0
1	1	1	0	0	0	0	0	0	0	4	0
0	0	0	0	1	1	0	0	0	0	1	1
1	1	1	0	1	1	0	0	0	0	4	1
0	0	0	0	0	0	0	0	0	0	1	0
0	0	0	0	0	0	1	0	0	0	1	1
0	0	0	0	1	1	1	0	0	0	4	1
1	1	1	0	0	0	0	0	0	0	4	0
1	1	1	0	0	1	1	0	0	0	4	1
0	0	0	0	0	1	0	1	1	0	1	1
1	1	1	1	1	1	0	0	0	0	1	1

ANNEXURE VI

ETHICAL COMMITTEE APPROVAL SHEET

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To

Dr.P.Venkatesh,
P.G in Neurology,
Madras Medical College, Chennai -3

Dear Dr.P.Venkatesh,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Anti Ganglioside Antibody profile in GBS – Clinical, Immunological and Neurophysiological Significance" No.19022013.

The following members of Ethics Committee were present in the meeting held on 05.02.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.SivaKumar, MS FICS FAIS	--- Chairperson
2. Prof. R. Nandhini MD Director, Instt. of Pharmacology ,MMC, Ch-3	-- Member Secretary
3. Prof. Shyamraj MD Director i/c , Instt. of Biochemistry , MMC, Ch-3	-- Member
4. Prof. P. Karkuzhali. MD Prof., Instt. of Pathology, MMC, Ch-3	-- Member
5. Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member
6. Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
7. Thiru. S. Govindsamy. BABL	-- Lawyer
8. Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

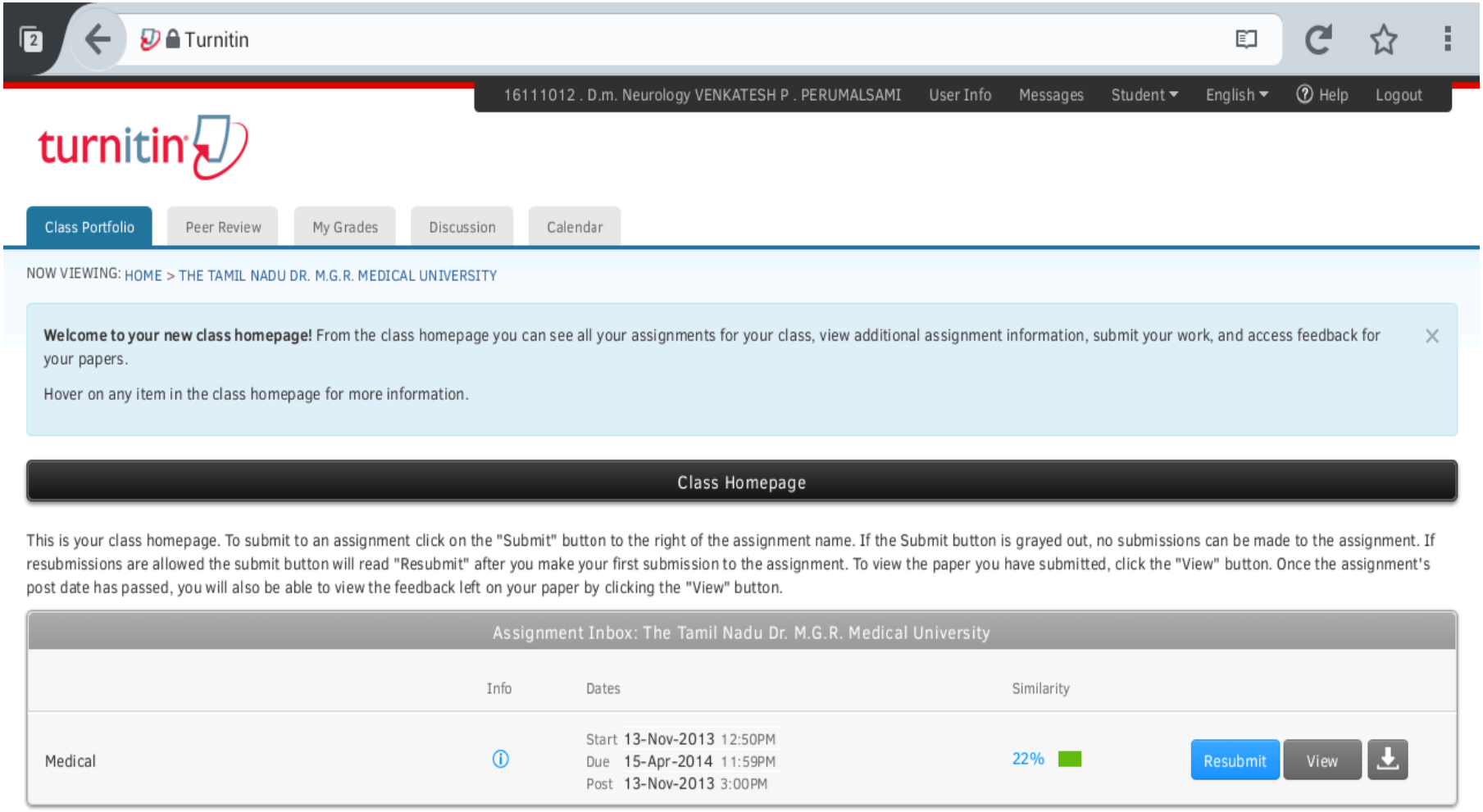
The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nadini
Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

ANNEXURE VII

TURNITIN-PLAGIARISM SCREEN SHOT



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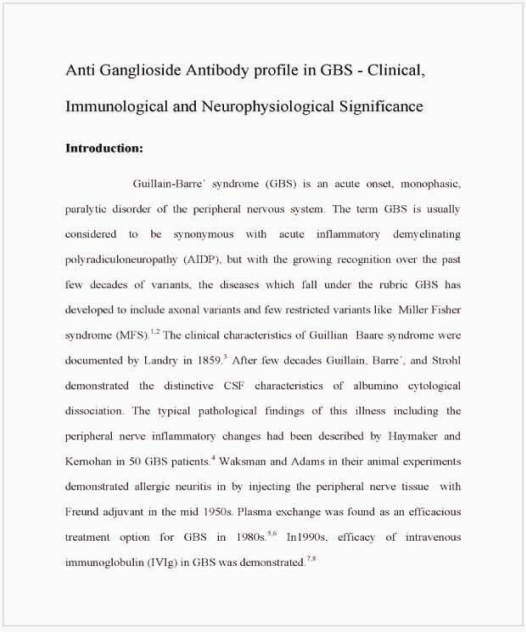

Anti Ganglioside Antibody profile in GBS - Clinical, Immunological and Neurophysiological Significance

Introduction:

Guillain-Barre' syndrome (GBS) is an acute onset, monophasic, paralytic disorder of the peripheral nervous system. The term GBS is usually considered to be synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but with the growing recognition over the past few decades of variants, the diseases which fall under the rubric GBS has developed to include axonal variants and few restricted variants like Miller Fisher syndrome (MFS).[1,2] The clinical characteristics of Guillian Baare syndrome were documented by Landry in 1859.[3] After few decades Guillain, Barre', and Strohl demonstrated the distinctive CSF characteristics of albumino cytological dissociation. The typical pathological findings of this illness including the peripheral nerve inflammatory changes had been described by Haymaker and Kernohan in 50 GBS patients.[4] Waksman and Adams in their animal experiments demonstrated allergic neuritis in by injecting the peripheral nerve tissue with Freund adjuvant in the mid 1950s. Plasma exchange was found as an efficacious treatment option for GBS in 1980s.[5,6] In1990s, efficacy of intravenous immunoglobulin (IVIg) in GBS was demonstrated.[7,8]